

This Declaration with the attached Exhibits are being submitted in conjunction with the Applicants' Response to the Office Action dated May 26, 2004.

I, Yasumich Hitoshi, M.D. Ph.D., do hereby declare as follows.

- I am currently a program director at Rigel Pharmaceuticals, Inc. (hereinafter "Rigel"), and the work described in the above-referenced patent application was performed with my knowledge.
- 2. I understand that the claimed subject matter of the above-referenced patent application relates to assays for identifying agents that modulate the poly(A) ribose polymerase activity of Tankyrase H.
- I have been asked to provide factual evidence relating to the activities of Rigel and Rigel's patent counsel with respect to the claimed subject matter, prior to October 25, 1999 (the filing date of the above-referenced patent application).



- 4. I have reviewed the Exhibits attached hereto and they all relate to the activities of Rigel or Rigel's patent counsel with respect the claimed subject matter, prior to October 25, 1999.
- 5. Prior to June 11, 1999, the inventors of the above-referenced patent application identified the sequence of the ADP-ribose polymerase domain of Tankyrase H and identified that Tankyrase H had poly(A) ribose polymerase activity. Evidence for this is provided in Exhibit A. All redacted dates are prior to June 11, 1999.
- 6. Further, between June 11, 1999, and July 21 1999, the inventors worked towards identifying the full length sequence of Tankyrase H for use in the above-referenced screening assays. Evidence for this is provided in Exhibits B and C. The dates have not been redacted in these exhibits.
- 7. Finally, between July 20, 1999 and October 25, 1999, the above-referenced patent application was drafted at the law firm of Flehr, Hobach, Test, Albritton and Herbert (hereinafter "Flehr), the law firm contracted to draft the above-referenced patent application. Evidence for this is provided in Exhibits D H. The dates have not been redacted in these exhibits.
- 8. Exhibit A consists of a print-out of Tankyrase H amino acid and nucleic acid sequences. On pages, 2, 6 and 7 of this Exhibit, Tankyrase H is identified as having a poly(A) ribose polymerase domain. The date of the print-out was prior to June 11, 1999.
- 9. Exhibit B consists of a presentation that was made by Xiang Xu, an inventor, that identifies Tankyrase H as having poly(A) ribose polymerase activity on page 3. The date of this presentation was June 15, 1999.
- 10. Exhibit C consists of signed laboratory notebook pages from Simon Yu, a colleague at Rigel Pharmaceuticals, Inc. These notebook pages show results of experiments directed towards identifying the full length sequence of Tankyrase H for use in the above-

referenced screening assays. The notebook pages are dated July 9, July 13, July 15, July 16 and July 21, 1999, respectively.

- 11. Exhibit D consists of a letter from Nicole Verona of Rigel to Ms. Robin Silva of Flehr), the law firm contracted to draft the above-referenced patent application. The letter references an invention disclosure (i.e., eight packages of information) for use in preparation of the above-referenced patent application. The date of the letter is July 20, 1999.
- 12. Exhibit E consists of a letter from Nicole Verona of Rigel to Ms. Robin Silva of Flehr. The letter references diskettes for use in preparation of the above-referenced patent application. The date of the letter is July 22, 1999.
- 13. Exhibit F consists of a file information page from Flehr, indicating that the file for the above-referenced patent application was opened on July 26, 2003.
- 14. Exhibit G consists of an e-mail dated August 30, 1999, from Nicole Verona of Rigel to Ms. Dolly Vance of Flehr regarding questions about the above referenced invention disclosure. The body of this e-mail contains text of previous e-mails dated August 20, 1999 and August 26, 1999, also relating to the above referenced invention disclosure.
- 15. Exhibit H consists of a letter from Nicole Verona of Rigel to Ms. Dolly Vance regarding further documents for use in drafting the above-referenced patent application. The date of the letter is September 30, 1999.
- 16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18

of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: 9/3/04

Yasumichi Hitoshi, M.D. Ph.D.,

Attachments: Exhibits A - G

Exhibit A 09/843,159
in XXU (ummon & final

3rd Assembly

Longest ORF frame 1 of 1060 amino acids

From amino acid position 84 to 1143

- MVQTPMLEIIGIILLSMKLQLKERLMFALCCYFAVLLOHGAEPTILNTDGRTALDLADPS
- AKAVLTGEYKKDELLESARSGNEEKMMALLTPLNVNCHASDGRKSTPLHLAAGYNRVKIV
- 121 QLLLQHGADVHAKDKGDLVPLHNACSYGHYEVTELLVKHGACVNAMDLWQFTPLHEAASK
- 181 NRVEVCSLLLSYGADPTLLNCHNKSAIDLAPTPQLKERLAYEFKGHSLLQAAREADVTRI
- 241 KKHLSLEMVNFKHPQTHETALHCAAASPYPKRKQICELLLRKGANINEKTKEFLTPLHVA
- 301 SEKAHNDVVEVVVKHEAKVNALDNLGQTSLHRAAYCGHLQTCRLLLSYGCDPNIISLQGF
- 361 TALQMGNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGROS
- 421 TPLHFAAGYNRVSVVEYLLQHGADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVVNV
- 481 ADLWKFTPLHEAAAKGKYEICKLLLQHGADPTKKNRDGNTPLDLVKDGDTDIHYLLRGDA
- 541 ALLDAAKKGCLARVKKLSSPDNVNCRDTQGRHSTPLHLAAGYNNLEVAEYLLQHGADVNA
- 601 QDKGGLIPLHNAASYGHVDVAALLIKYNACVNATDKWAFTPLHEAAOKGRTOLCALLLAH 661 GADPTLKNQEGQTPLDLVSADDVSALLTAAMPPSALPSCYKPQVLNGVRSPGATADALSS
- 721 GPSSPSSLSAASSLDNLSGSFSELSSLVSSSGTEGASSLEKKEVPGVDFSITQFVRNLGL
- 781 EHLMDIFEREQITLDVLVEMGHKELKEIGINAYGHRHKLIKGVERLISGOOGLNPYLTLN
- 841 TSGSGTILIDLSPDDKEFQSVEEEMQSTVREHRDGGHAGGIFNRYNILKIOKVCNKKLWE
- 901 RYTHRRKEVSEENHNHANERMLFHGSPFVNAIIHKGFDERHAYIGGMFGAGIYFAENSSK
- 961 SNQYVYGIGGGTGCPVHKDRSCYICHRQLLFCRVTLGKSFLQFSAMKMAHSPPGHHSVTG
- 1021 RPSVNGLALAEYVIYRGEQAYPEYLITYQIMRPEGMVDGZ
- GAAGTGCAGCGGGGTGGATTTCCTGGAATTGCCTTAGTAGTAGTACCACCCAAGGCACTG
- CTTAGGTACCACTGCTTAGTGGAGAGTCCCTCTGGCTTTATCATTAAGGTTTTGGGC
- 121 GGAAAGACGTAGTTGAATATTTGCTTCAGAATGGTGCAAATGTCCAAGCACGTGATGATG
- 181 GGGGCCTTATTCCTCTTCATAATGCATGCTCTTTTGGTCATGCTGAAGTAGTCAATCTCC
- 241 TTTTGCGACATGGTGCAGACCCCAATGCTCGAGATAATTGGAATTATACTCCTCTCCATG
- 301 AAGCTGCAATTAAAGGAAAGATTGATGTTTGCATTGTGTTGCTATTTTGCAGTGCTGTTA
- 361 CAGCATGGAGCTGAGCCAACCATCCTAAATACAGATGGAAGGACAGCATTGGATTTAGCA
- 481 GCCAGGAGTGGCAATGAAGAAAAATGATGGCTCTACTCACACCATTAAATGTCAACTGC
- 541 CACGCAAGTGATGGCAGAAAGTCAACTCCATTACATTTGGCAGCAGGATATAACAGAGTA
- 601 AAGATTGTACAGCTGTTACTGCAACATGGAGCTGATGTCCATGCTAAAGATAAAGGTGAT
- 661 CTGGTACCATTACACAATGCCTGTTCTTATGGTCATTATGAAGTAACTGAACTTTTGGTC
- 721 AAGCATGGTGCCTGTGTAAATGCAATGGACTTGTGGCAATTCACTCCTCTTCATGAGGCA
- 781 GCTTCTAAGAACAGGGTTGAAGTATGTTCTCTTCTCTTAAGTTATGGTGCAGACCCAACA
- 841 CTGCTCAATTGTCACAATAAAAGTGCTATAGACTTGGCTCCCACACCACAGTTAAAAGAA
- 901 AGATTAGCATATGAATTTAAAGGCCACTCGTTGCTGCAAGCTGCACGAGAAGCTGATGTT
- 961 ACTCGAATCAAAAAACATCTCTCTCTGGAAATGGTGAATTTCAAGCATCCTCAAACACAT
- 1081 CTGTTGCTAAGAAAAGGAGCAAACATCAATGAAAAGACTAAAGAATTCTTGACTCCTCTG
- 1141 CACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACATGAAGCA
- 1201 AAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATATTGTGGT 1261 CATCTACAAACCTGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATATCCCTT
- 1321 CAGGGCTTTACTGCTTTACAGATGGGAAATGAAAATGTACAGCAACTCCTCCAAGAGGGT
- 1381 ATCTCATTAGGTAATTCAGAGGCAGACAGACAATTGCTGGAAGCTGCAAAGGCTGGAGAT
- 1441 GTCGAAACTGTAAAAAAACTGTGTACTGTTCAGAGTGTCAACTGCAGAGACATTGAAGGG
- 1501 CGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAATAT
- 1561 CTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCTTGTACCTTTGCAC
- 1621 AATGCATGTTCTTATGGACATTATGAAGTTGCAGAACTTCTTGTTAAACATGGAGCAGTA
- 1681 GTTAATGTAGCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAAGGAAAA
- 1801 GGAAATACTCCTTTGGATCTTGTTAAAGATGGAGATACAGATATTCATTATCTGCTTAGG
- 1861 GGAGATGCAGCTTTGCTAGATGCTCCCAAGAAGGTTGTTTAGCCAGAGTGAAGAAGTTG 1921 TCTTCTCCTGATAATGTAAATTGCCGCGATACCCAAGGCAGACATTCAACACCTTTACAT

1981 TTAGCAGCTGGTTATAATAATTTAGAAGTTGCAGAGTATTTGTTACAACACGGAGCTGAT 2041 GTGAATGCCCAAGACAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTACGGGCAT 2101.GTAGATGTAGCAGCTCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGACAAATGG 2161 GCTTTCACACCTTTGCACGAAGCAGCCCAAAAGGGACGAACACAGCTTTGTGCTTTGTTG 2281 GTTTCAGCGGATGATGTCAGCGCTCTTCTGACAGCAGCCATGCCCCCATCTGCTCTGCCC 2341 TCTTGTTACAAGCCTCAAGTGCTCAATGGTGTGAGAAGCCCAGGAGCCACTGCAGATGCT 2461 TCTGGGAGTTTTTCAGAACTGTCTTCATTAGTTAGTTCAAGTGGAACAGAGGGTGCTTCC 2521 AGTTTGGAGAAAAAGGAGGTTCCAGGAGTAGATTTTAGCATAACTCAATTCGTAAGGAAT 2581 CTTGGACTTGAGCACCTAATGGATATATTTGAGAGAGAACAGATCACTTTGGATGTATTA 2641 GTTGAGATGGGGCACAAGGAGCTGAAGGAGATTGGAATCAATGCTTATGGACATAGGCAC 2701 AAACTAATTAAAGGAGTCGAGAGACTTATCTCCGGACAACAAGGTCTTAACCCATATTTA 2761 ACTTTGAACACCTCTGGTAGTGGAACAATTCTTATAGATCTGTCTCCTGATGATAAAGAG 2821 TTTCAGTCTGTGGAGGAAGAGATGCAAAGTACAGTTCGAGAGCACAGAGATGGAGGTCAT 2881 GCAGGTGGAATCTTCAACAGATACAATATTCTCAAGATTCAGAAGGTTTGTAACAAGAAA 2941 CTATGGGAAAGATACACTCACCGGAGAAAAGAAGTTTCTGAAGAAAACCACAACCATGCC 3001 AATGAACGAATGCTATTTCATGGGTCTCCTTTTGTGAATGCAATTATCCACAAAGGCTTT 3121 TCTTCCAAAAGCAATCAATATGTATATGGAATTGGAGGAGGTACTGGGTGTCCAGTTCAC 3181 AAAGACAGATCTTGTTACATTTGCCACAGGCAGCTGCTCTTTTGCCGGGTAACCTTGGGA 3241 AAGTCTTTCCTGCAGTTCAGTGCAATGAAAATGGCACATTCTCCTCCAGGTCATCACTCA 3301 GTCACTGGTAGGCCCAGTGTAAATGGCCTAGCATTAGCTGAATATGTTATTTACAGAGGA 3361 GAACAGGCTTATCCTGAGTATTTAATTACTTACCAGATTATGAGGCCTGAAGGTATGGTC 3421 GATGGATAAATAGTTATTTTAAGAAACTAATTCCACTGAACCTAAAATCATCAAAGCAGC

ref|NP_003738.1|PTNKS| TANKYRASE >gi|3929219 (AF082556) TRF1-interacting ankyrin-related ADP-ribose polymerase [Homo sapiens] Length = 1327Score = 1640 bits (4199), Expect = 0.0Identities = 790/1023 (77%), Positives = 871/1023 (84%), Gaps = 11/1023 (1%) VLLQHGAEPTILNTDGRTALDLADPSAKAVLTGEYKKDELLESARSGNEEKMMALLTPLN 94 Query: 35 VLLQHGA+P I NTDG++ALDLADPSAKAVLTGEYKKDELLE+ARSGNEEK+MALLTPLN VLLQHGADPNIRNTDGKSALDLADPSAKAVLTGEYKKDELLEAARSGNEEKLMALLTPLN 359 Sbjct: 300 VNCHASDGRKSTPLHLAAGYNRVKIVQLLLQHGADVHAKDKGDLVPLHNACSYGHYEVTE 154 Query: 95 VNCHASDGRKSTPLHLAAGYNRV+IVQLLLQHGADVHAKDKG LVPLHNACSYGHYEVTE VNCHASDGRKSTPLHLAAGYNRVRIVQLLLQHGADVHAKDKGGLVPLHNACSYGHYEVTE 419 Sbjct: 360 Query: 155 LLVKHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLSYGADPTLLNCHNKSAIDLAPTPQ 214 LL+KHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLS+GADPTL+NCH KSA+D+APTP+ Sbjct: 420 LLLKHGACVNAMDLWQFTPLHEAASKNRVEVCSLLLSHGADPTLVNCHGKSAVDMAPTPE 479 Query: 215 LKERLAYEFKGHSLLQAAREADVTRIKKHLSLEMVNFKHPQTHETALHCAAASPYPKRKQ 274 L+ERL YEFKGHSLLQAAREAD+ ++KK L+LE++NFK PQ+HETALHCA AS +PKRKQ Sbjct: 480 LRERLTYEFKGHSLLQAAREADLAKVKKTLALEIINFKQPQSHETALHCAVASLHPKRKQ 539 ICELLLRKGANINEKTKEFLTPLHVASXXXXXXXXXXXXXXXXXXXXXLDNLGQTSLHRAA 334 Query: 275 LD LGQT+LHRAA + ELLLRKGAN+NEK K+F+TPLHVA+ Sbjct: 540 VTELLLRKGANVNEKNKDFMTPLHVAAERAHNDVMEVLHKHGAKMNALDTLGQTALHRAA 599 Query: 335 YCGHLQTCRLLLSYGCDPNIISLQGFTALQMGNENVQQLLQEGISLGNSEADRQLLEAAK 394 + S+ D +LLEA+K GHLOTCRLLLSYG DP+IISLQGFTA QMGNE VQQ+L E Sbjct: 600 LAGHLQTCRLLLSYGSDPSIISLQGFTAAQMGNEAVQQILSESTPIRTSDVDYRLLEASK 659

Query:	395	AGDVETVKKLCTVQSVNCRDIEGRQSTPLHFAAGYNRVSVVEYLLQHGADVHAKDKGGLV AGD+ETVK+LC+ Q+VNCRD+EGR STPLHFAAGYNRVSVVEYLL HGADVHAKDKGGLV	454
Sbjct:	660	AGDLETVKQLCSSQNVNCRDLEGRHSTPLHFAAGYNRVSVVEYLLHHGADVHAKDKGGLV	719
Query:	455	PLHNACSYGHYEVAELLVKHGAVVNVADLWKFTPLHEAAAKGKYEICKLLLQHGADPTKK PLHNACSYGHYEVAELLV+HGA VNVADLWKFTPLHEAAAKGKYEICKLLL+HGADPTKK	514 .
Sbjct:	720	PLHNACSYGHYEVAELLVRHGASVNVADLWKFTPLHEAAAKGKYEICKLLLKHGADPTKK	779
Query:	515	NRDGNTPLDLVKDGDTDIHYXXXXXXXXXXXXXXXXXXXXXXVKKLSSPDNVNCRDTQGRHST NRDGNTPLDLVK+GDTDI RV+KL +P+N+NCRDTQGR+ST	574
Sbjct:	780	NRDGNTPLDLVKEGDTDIQDLLKGDAALLDAAKKGCLARVQKLCTPENINCRDTQGRNST	839
Query:	575	PLHLAAGYNNLEVAEYLLQHGADVNAQDKGGLIPLHNAASYGHVDVAALLIKYNACVNAT PLHLAAGYNNLEVAEYLL+HGADVNAQDKGGLIPLHNAASYGHVD+AALLIKYN CVNAT	634
Sbjct:	840	PLHLAAGYNNLEVAEYLLEHGADVNAQDKGGLIPLHNAASYGHVDIAALLIKYNTCVNAT	899
Query:	635	DKWAFTPLHEAAQKGRTQLCALLLAHGADPTLKNQEGQTPLDLVSADDVSALLTAAMPPS DKWAFTPLHEAAQKGRTQLCALLLAHGADPT+KNQEGQTPLDL +ADD+ ALL AMPP	694
Sbjct:	900	DKWAFTPLHEAAQKGRTQLCALLLAHGADPTMKNQEGQTPLDLATADDIRALLIDAMPPE	959
Query:	695	ALPSCYKPQVLNGVRSPGATXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	751
Sbjct:	960	ALPTCFKPQATVVSASLISPASTPSCLSAASSIDNLTGPLAELAVGGASNAG	1011
Query:	752	XXXXXXXXKKEVPGVDFSITQFVRNLGLEHLMDIFEREQITLDVLVEMGHKELKEIGIN + EV G+D +1+QF+++LGLEHL DIFE EQITLDVL +MGH+ELKEIGIN	811
Sbjct:	1012	DGAAGTERKEGEVAGLDMNISQFLKSLGLEHLRDIFETEQITLDVLADMGHEELKEIGIN	1071
Query:	812	AYGHRHKLIKGVERLISGQQGLNPYLTLNTSGSGTILIDLSPDDKEFQSVEEEMQSTVRE AYGHRHKLIKGVERL+ GQQG NPYLT + GTIL+DL+P+DKE+QSVEEEMQST+RE	871
Sbjct:	1072	AYGHRHKLIKGVERLLGGQQGTNPYLTFHCVNQGTILLDLAPEDKEYQSVEEEMQSTIRE	1131
Query:	872	HRDGGHAGGIFNRYNILKIQKVCNKKLWERYTHRRKEVSEENHNHANERMLFHGSPFVNA HRDGG+AGGIFNRYN+++IQKV NKKL ER+ HR+KEVSEENHNH NERMLFHGSPF+NA	931
Sbjct:	1132	HRDGGNAGGIFNRYNVIRIQKVVNKKLRERFCHRQKEVSEENHNHHNERMLFHGSPFINA	1191
Query:	932	IIHKGFDERHAYIGGMFGAGIYFAENSSKSNQYVYGIGGGTGCPVHKDRSCYICHRQLLF IIHKGFDERHAYIGGMFGAGIYFAENSSKSNQYVYGIGGGTGCP HKDRSCYICHRQ+LF	991
Sbjct:	1192	IIHKGFDERHAYIGGMFGAGIYFAENSSKSNQYVYGIGGGTGCPTHKDRSCYICHRQMLF	1251
Query:	992	CRVTLGKSFLQFSAMKMAHSPPGHHSVTGRPSVNGLALAEYVIYRGEQAYPEYLITYQIM CRVTLGKSFLQFS MKMAH+PPGHHSV GRPSVNGLA AEYVIYRGEQAYPEYLITYQIM	
Sbjct:	1252	CRVTLGKSFLQFSTMKMAHAPPGHHSVIGRPSVNGLAYAEYVIYRGEQAYPEYLITYQIM	
Query:	1052	RPE 1054 +PE	
Sbjct:	1312	KPE 1314	

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- 61 GCTGAGCCAACCR10ATCCTAAATACAGATGGAAGGACAGCATTGGR9ATTTAGCAGATCCATCT
- 121 GCCAAAGCAGTGR8CTTACTGGTGAATATAAGAAAGATGAACTCTTAGAAAGTGCCAGGAGT

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361 TTACACAATGCCTGTTCTTATGGTCATTATGAAGTAACTGAACTTTTGGTCAAGCATGGT
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1381 GCTGATTTATGGAAATTTACACCTTTACATGAAGCAGCAGCAAAAGGAAAATATGAAATT
1501 CCTTTGGATCTTGTTAAAGATGGAGATACAGATATTCATTATCTGCTTAGGGGAGATGCA
1561 GCTTTGCTAGATGCTGCCAAGAAGGGTTGTTTAGCCAGAGTGAAGAAGTTGTCTTCTCCT
1621 GATAATGTAAATTGCCGCGATACCCAAGGCAGACATTCAACACCTTTACATTTAGCAGCT
1681 GGTTATAATAATTTAGAAGTTGCAGAGTATTTGTTACAACACGGAGCTGATGTGAATGCC
1741 CAAGACAAAGGAGGACTTATTCCTTTACATAATGCAGCATCTTACGGGCATGTAGATGTA
1801 GCAGCTCTACTAATAAAGTATAATGCATGTGTCAATGCCACGGACAAATGGGCTTTCACA
1861 CCTTTGCACGAAGCAGCCCAAAAGGGACGAACACACCTTTGTGCTTTGTTGCTAGCCCAT
1921 GGAGCTGACCCGACTCTTAAAAATCAGGAAGGACAAACACCTTTAGATTTAGTTTCAGCG
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2041 AAGCCTCAAGTGCTCAATGGTGTGAGAAGCCCAGGAGCCACTGCAGATGCTCTCTTCA
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2161 TTTTCAGAACTGTCTTCATTAGTTAGTTCAAGTGGAACAGAGGGTGCTTCCAGTTTGGAG
2221 AAAAAGGAGGTTCCAGGAGTAGATTTTAGCATAACTCAATTCGTAAGGAATCTTGGACTT
2281 GAGCACCTAATGGATATTTTGAGAGAGAACAGATCACTTTGGATGTATTAGTTGAGATG
2341 GGGCACAAGGAGCTGAAGGAGATTGGAATCAATGCTTATGGACATAGGCACAAACTAATT
2401 AAAGGAGTCGAGAGACTTATCTCCGGACAACAAGGTCTTAACCCATATTTAACTTTGAAC
2461 ACCTCTGGTAGTGGAACAATTCTTATAGF5ATCTGTCTCCTGATGATAAAGAGTTTCAGTCTF6
2521 GTGGAGGAAGAGATGCAAAGTACAGTTCGAGAGCACAGAGAF7TGGAGGTCATGCAGGTGGA
2581 ATCTTCAACAGATACAATATTCTCAAGATTCAGAAGGTTTGTAACA
, Plus
```

3'end

GTCTCCTGATGATAAAGAGTTTCAGTCTGTGGAGGAAGAGATGCAAAGT ACAGTTCGAGAGCACAGAGATGGAGGTCATGCAGGTGGAATCTTC AACAGATACAATATTCTCAAGATTCAGAAGGTTTGTAACAAGAAACTATGGGA AAGATACACTCACCGGAGAAAAGAAGTTTCTGAAGAAAACCACAACCATGCCAATGA ACGAATGCTATTTCATGGGTCTCCTTTTGTGAATGCAATTATCCACAAAGGCTTTGATG CCAAAAGCAATCAATATGTATATGGAATTGGAGGAGGTACTGGGTGTCCAGTTCACAAAG ACAGATCTTGTTACATTTGCCACAGGCAGCTGCTCTTTTGCCGGGTAACCTTGGGAAAG TCTTTCCTGCAGTTCAGTGCAATGAAAATGGCACATTCTCCTCCAGGTCATCACTCAGTC ACTGGTAGGCCCAGTGTAAATGGCCTAGCATTAGCTGAATATGTTATTTACAGAGGAGAA CAGGCTTATCCTGAGTATTTAATTACTTACCAGATTATGAGGCCTGAAGGTATGGTCG ATGGATAAATAGTTATTTTAAGAAACTAATTCCACTGAACCTAAAATCATCAAAGCAGC

- gi|3929219 (AF082556) TRF1-interacting ankyrin-related ADP-ribose polymerase Length = 1327 · [Homo sapiens] Score = 464 bits (1181), Expect = e-130 Identities = 223/309 (72%), Positives = 249/309 (80%) Frame = +2 LEMVNFKHPQTHETALHCAAASPYPKRKQICELLLRKGANINEKTKEFLTPLHVASXXXX 181 LE++NFK PO+HETALHCA AS +PKRKQ+ ELLLRKGAN+NEK K+F+TPLHVA+ Sbjct: 511 LEIINFKQPQSHETALHCAVASLHPKRKQVTELLLRKGANVNEKNKDFMTPLHVAAERAH 570 Ouery: 182 XXXXXXXXXXXXXXXLDNLGQTSLHRAAYCGHLQTCRLLLSYGCDPNIISLQGFTALQM 361 LD LGOT+LHRAA GHLQTCRLLLSYG DP+IISLQGFTA QM Sbjct: 571 NDVMEVLHKHGAKMNALDTLGQTALHRAALAGHLQTCRLLLSYGSDPSIISLQGFTAAQM 630 Query: 362 GNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHF 541 + S+ D +LLEA+KAGD+ETVK+LC+ Q+VNCRD+EGR STPLHF GNE VOO+L E Sbjct: 631 GNEAVOOILSESTPIRTSDVDYRLLEASKAGDLETVKQLCSSQNVNCRDLEGRHSTPLHF 690 Query: 542 AAGYNRVSVVEYLLQHGADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVVNVADLWK 721 AAGYNRVSVVEYLL HGADVHAKDKGGLVPLHNACSYGHYEVAELLV+HGA VNVADLWK. Sbjct: 691 AAGYNRVSVVEYLLHHGADVHAKDKGGLVPLHNACSYGHYEVAELLVRHGASVNVADLWK 750 Query: 722 FTPLHEAAAKGKYEICKLLLQHGADPTKKNRDGNTPLDLVKDGDTXIQXXXXXXXXXXX 901 FTPLHEAAAKGKYEICKLLL+HGADPTKKNRDGNTPLDLVK+GDT IQ Sbjct: 751 FTPLHEAAAKGKYEICKLLLKHGADPTKKNRDGNTPLDLVKEGDTDIQDLLKGDAALLDA 810 Query: 902 XXKGCFXQI 928 KGC ++ Sbjct: 811 AKKGCLARV 819 Longest ORF frame 2 of 310 amino acids
- From amino acid position 1 to 311
- ${\tt LEMVNFKHPQTHETALHCAAASPYPKRKQICELLLRKGANINEKTKEFLTPLHVASEKAH}$
- 61 NDVVEVVVKHEAKVNALDNLGQTSLHRAAYCGHLQTCRLLLSYGCDPNIISLQGFTALQM
- 121 GNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEGRQSTPLHF
- 181 AAGYNRVSVVEYLLQHGADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAVVNVADLWK
- 241 FTPLHEAAAKGKYEICKLLLQHGADPTKKNRDGNTPLDLVKDGDTXIQDLLRGDAXXLDA
- 301 AXKGCFXQIX
- GCTGGAAATGGTGAATTTCAAGCATCCTCAAAR7CACATGAAACAGCATTGCATTGTGCTGC
- TGCATCTCCATATCCCAAAAGAAAGCAAAR6TATGTGAACTGTTGCTAAGAAAAGGAGCAAA
- 121 R5CATCAATGAAAAGACTAAAGAATTCTTGACTCCTCTGCACGTGGCATCTGAGAAAGCTCA
- 181 TAATGATGTTGTTGAAGTAGTGGTGAAACATGAAGCAAAGGTTAATGCTCTGGATAATCT
- 241 TGGTCAGACTTCTCTACACAGAGCTGCATATTGTGGTCATCTACAAACCTGCCGCCTACT
- 301 CCTGAGCTATGGGTGTGATCCTAACATTATATCCCTTCAGGGCTTTACTGCTTTACAGAT
- 361 GGGAAATGAAAATGTACAGCAACTCCTCCAAGAGGGTATCTCATTAGGTAATTCAGAGGC
- 421 AGACAGACAATTGCTGGAAGCTGCAAAGGCTGGAGATGTCGAAACTGTAAAAAAACTGTG
- 481 TACTGTTCAGAGTGTCAACTGCAGAGACATTGAAGGGCGTCAGTCTACACCACTTCATTT
- 541 TGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAATATCTGCTACAGCATGGAGCTGATGT
- 601 GCATGCTAAAGATAAAGGAGGCCTTGTACCTTTGCACAATGCATGTTCTTATGGACATTA
- 661 TGAAGTTGCAGAACTTCTTGTTAAACATGGAGCAGTAGTTAATGTAGCTGATTTATGGAA
- 721 ATTTACACCTTTACATGAAGCAGCAGCAAAAGGAAAATATGAAATTTGCAAACTTCTGCT
- 781 CCAGCATGGTGCAGACCCTACCAAAAAAACAGGGATGGAAATACTCCTTTGGATCTTGT 841 TAAAGATGGAGATACANATATTCAAGATCTGCTTAGGGGAGATGCANNTTTNCTAGATGC
- 901 TGCCNANAAGGGTTGTTTTANCCAGATTNAA

>EST assembled Good protein homology to gi 3929221 (AF082557) TRF1-interacting ankyrin-related ADP-ribose polymerase [Homo sapiens] TITLE Tankyrase, a poly(ADP-ribose) polymerase at human telomeres JOURNAL Science 282, 1484-1487 (1998) Longest ORF frame 3 of 258 amino acids HVASEKAHNDVVEVVVKHEAKVNALDNLGQTSLHRAAXCGHLQTCRLLLSYGCDPNIISL QGFTALQMGNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEG

QGFTALQMGNENVQQLLQEGISLGNSEADRQLLEAAKAGDVETVKKLCTVQSVNCRDIEG RQSTPLHFAAGYNRVSVVEYLLQHGADVHAKDKGGLVPLHNACSYGHYEVAELLVKHGAV VNVADLWKFTPLHEAAAKGKYEICKLLLQHGADPTKKNRDGNTPLDLVKDGDTXIQDLLR GDAXXLDAAXKGCFXQIX

TGCACGTGGCATCTGAGAAAGCTCATAATGATGTTGTTGAAGTAGTGGTGAAACATGAAG
R2CAAAGGTTAATGCTCTGGATAATCTTGGTCAGACTTCTCTACACAGAGCTGCATNTTGTG
GNCATCTACAAACCR1TGCCGCCTACTCCTGAGCTATGGGTGTGATCCTAACATTATATCCC
TTCAGGGCTTTACTGCTTTACAGATGF4GGAAATGAAAATGTACAGCAACTCCTCCAAGAGG
GTATCTCATTAGGTAATTCAGAGGCAGACAGAR4CAATTGCTGGAAGCTGCAAAGGCTGGAG
ATGTCGAAACTGTAAAAAAACTGTGTACTGTTR3CAGAGTGTCAACTGCAGAGACATTGAAG
GGCGTCAGTCTACACCACTTCATTTTGCAGCTGGGTATAACAGAGTGTCCGTGGTGGAAT
ATCTGCTACAGCATGGAGCTGATGTGCATGCTAAAGATAAAGGAGGCCTTGTACCTTTGC
ACAATGCATGTTCTTATGGACATTATGAAGTTGCAGAACTTCTTGTTAAACATGGAGCAGF3
TAGTTAATGTAGCTGATTTATGGAAATTTACACCTTTTACATGAAGCAGCAGCAAAAGAAAAACAGGG
ATGGAAATACTCCTTTGGATCTTGTTAAF2AGATGGAGATACANATATTCAAGATCTGCTTA
GGGGAGATGCANNTTTNCTAGATGCTGCCNANAAGGGTTGTTTTANCCAGATTNAA

>cip6c1p5F2

TCATTATCTGCTTAGGGGAGATGCAGCTTT

GGATGGAAATACTCCTTTGGATCTTGTTAAAGATG

GAGATACAGATATTCAAGATCTGCTTAGGGGAGATGCAGCTTTGCTAGATGCTGCCAAGA
AGGGTTGTTTAGCCAGAGTGAAGAAGTTGTCTTCTCCTGATAATGTAAATTGCCGCGATA
CCCAAGGCAGACATTCAACACCTTTACATTTAGCAGCTGGTTATAATAATTTAGAAGTTG
CAGAGTATTTGTTACAACACGGAGCTGATGTGAATGCCCCAAGACAAAGGAGGACTTATTC
CTTTACATAATGCAGCATCTTACGGGCATGTAGATGTAGCAGCTCTACTAATAAAGTATA



Exh.b. + B 09/843,159 6/15/1969 W/ Tark northern blot

Chk1 two-hybrid screening

Bait: Chk1

is a protein kinase required for cell cycle arrest in response to DNA damage

Hit: a novel potein homology to ATP-dependent RNA helicase belongs to the DEAD-box RNA helicase family

The fission yeast cdc28(+) encodes a member of the DEAD-box family of putative RNA helicases involved in pre-mRNA splicing and cell cycle progression

a new gene encoding a putative DEAD box helicase have been isolated to suppress uncontrolled mitosis by overexpression cdc25 in fission yeast (Chk1 and 14-3-3 proteins also show up in this screening)

It is interesting to characterize the interaction of Chk1 and the novel RNA helicase and its role in cell cycle control

Potential targets for further pursuing

p21 hit:

Tankyrase homolog

Traf4 hit:

Cdk liked kinase

hRad9 hit:

PP5

PNCA hits:

a novel helicase

a human homolog of SNM1

a novel endo/exo-ribonuclease

Chk1 hit:

an ATP-dependent RNA helicase homolog

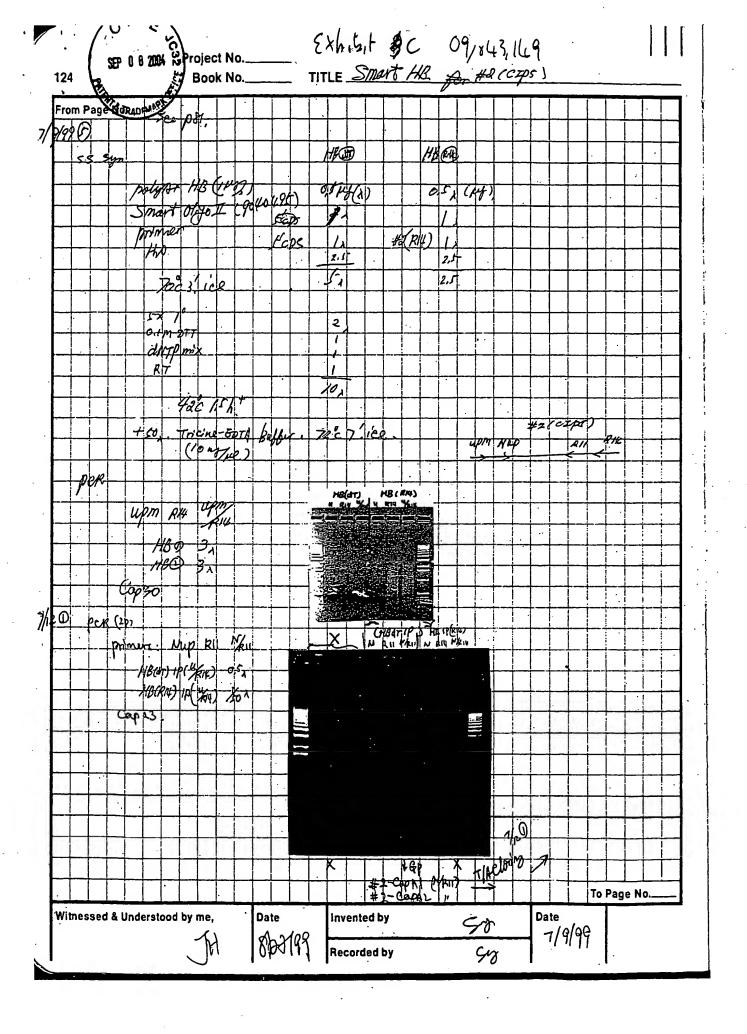
Target validation:

- ·full length cloning
- •examine the RNA expression in tumor verse normal tissues
- •peptide binding library screening in YTH---->functional assay
- •generate dominant-negative mutant .

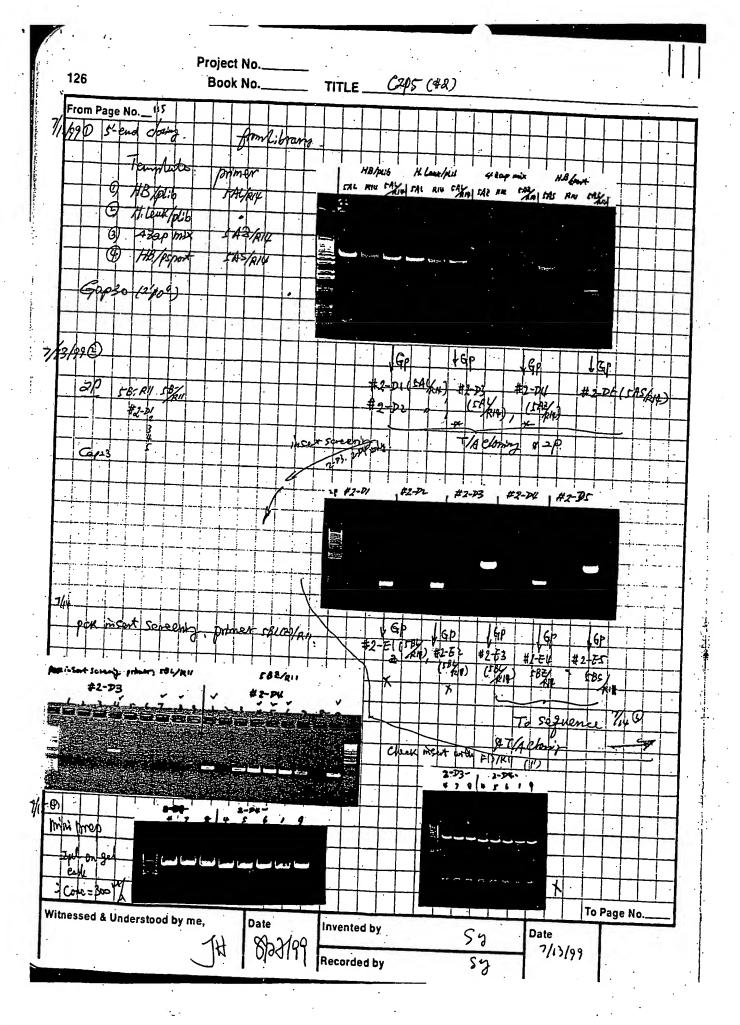
p21 hit: a Tankyrase homolog

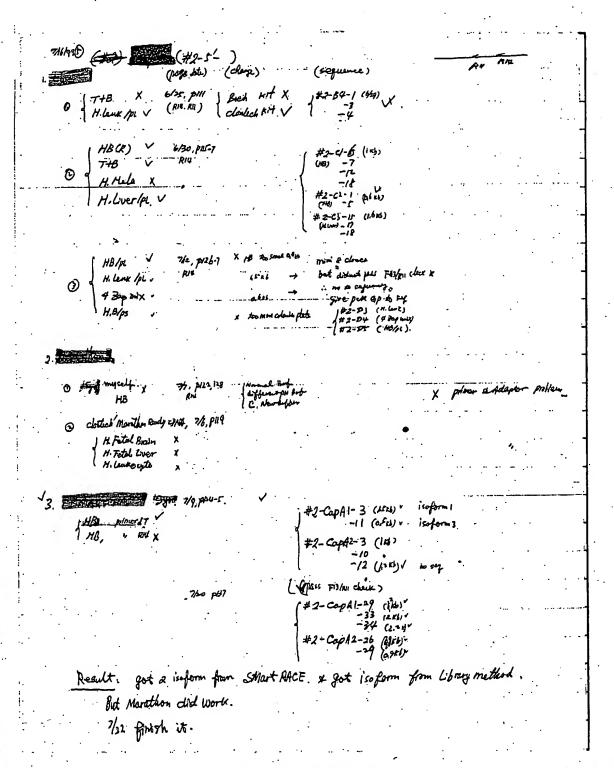
Tankyrase (a poly(ADP-ribose) polymerase at human telomeres)

- a protein with homology to ankyrin and to the catalytic domain of ADPribose polymerase (PARP)
- is localized to human telomeres
- binds to the telomeric protein TRF1 (telomeric repeat binding factor-1)
- is a positive regulator of telomere length maintenance

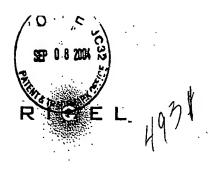


Project No. Book No. . 125 From Page No._ 118 (47) 148 (1814) 7/190 #3-CapAZ 10 11/2 Kesult 7/14 (1) no sequere 37 10 11 1 3 11 #2-COPAL- #2-COPAL- # 3 7 10 11 1- 13 11 227,000,05 To Page No. 137 Witnessed & Understood by me, Invented by Sy Date 8/27/99 7/13/99 JH Recorded by





SCIENTIFIC NOTEBOOK CO.



RIGEL, INC.

Exhibit D 09/843, 149

FLEHR, HOHBACH, TEST ALBRITTON & HERBERT

1999 JUL 22 AH 9. 02

REGENTED

July 20, 1999

VIA FEDERAL EXPRESS

Ms. Robin Silva Flehr, Hobach, Test, Albritton, & Herbert 4 Embarcadero Center, Suite 3400 San Francisco, California 94111-4187

PERRYS-OPEN AS WILLY

Re: Provisional Patent Applications.

Dear Ms. Silva,

Per Brian Cunningham's request, enclosed with this letter are eight packages of information generated by Dr. Ying Luo in preparation for provisional patent application filings. Each package pertains to a different genetic sequence that Rigel believes may be commercially useful. Each package contains relevant scientific materials, journal references and abstracts of proposed gene functions.

Please file a provisional patent application for each document.

If you have any questions, please call me at 650-624-1106.

Respectfully yours,

Nicole A. Verona

Rigel Pharmaceuticals, Inc.

240 East Grand Avenue South San Francisco, CA 94080 Main phone: 650.624.1100 Fax: 650.624.1101 http://www.rigel.com

Exhibit \$ E 09/847, 141

RIGEL

FLEHR, HOHBACH, TEST ALBRITTON & HERBERT

1999 JUL 23 AM 10: 04

RECEIVIED

July 22, 1999

VIA FEDERAL EXPRESS

Ms. Robin Silva Flehr, Hobach, Test, Albritton, & Herbert 4 Embarcadero Center, Suite 3400 San Francisco, California 94111-4187

P-68287

Re: Provisional Patent Applications.

Dear Ms. Silva.

It was a pleasure to meet you today. I'm sorry that I did not see you leave; I had intended to give you these diskettes before the end of our meeting.

On these diskettes are the documents that we reviewed earlier. The new document that Ying gave to me today will be ready on Monday.

If you have any questions, please call me at 650-624-1106.

Respectfully yours,

nuole Vero

Nicole A. Verona

Rigel Pharmaceuticals, Inc.

240 East Grand Avenue South San Francisco, CA 94080 Main phone: 650.624.1100 Fax: 650.624.1101 http://www.rigel.com

Exhibit &F 09/843,149

DOCKETING/BILLING SYSTEM FILE INFORMATION (Patent/Design Patent)

Date: July 26, 1999

File No.: A-68292

Client: Rigel Pharmaceuticals Access Code: 4931

Client

Attorney: DJB/RMS/DAV

Ref. No.:

New [X]

Update []

· Close []

Parent []

Div. []

CPA []

CIP []

Subject Description

Title:

TANKYRASEH, A Cell Cycle Protein

Inventors:

Ying Luo

Serial No.:

Filing Date:

Patent No.:

Issue Date:

Assignee:

Related Files:

If Foreign file, please provide corresponding U.S. Serial Number or Patent Registration Number.

Misc. (Include any action items and due dates here!):

Submitted by: Gail Clark

Date: July 26, 1999

cc: Accounting

Docketing - Foreign

Docketing - US

Zxhit 86.09843,149

From:

Nicole Verona <NVerona@rigel.com>

To:

"'dvance@flehr-iplaw.com'" <dvance@sfpo.fhtah.fleh...

8/30/99 4:01pm

Subject:

FW: FW: info

Dear Dolly,

I forwarded your questions to Ying Luo and this is the response I received from him. I hope this helps. Also, I've got copies of the TNIK manuscript figures that you need. Would you like me to fax them to you?

Nicole

----Original Message-----

From: Ying Luo [mailto:yluo@rigel.com] Sent: Sunday, August 29, 1999 2:44 PM.

To: Nicole Verona Subject: Re: FW: info

PAN is from PCNA screening. tankyraseH is from CIP screening. CIP is also called p21. R0101 has an entry in GenBank with full length sequence with a name called KIAA0101. No functional annotation about R0101. PP5 was cloned and published before. The novelty is we can link PP5 to RAD9, a cell cycle checkpoint control protein. You should have all figures of TNIK manuscript already. TNIK nucleotide sequences are attached. PAN nucleotide sequence is already in Genbank.

286 X

Ying

At 03:21 PM 8/26/99 -0700, you wrote:

>Hi Ying!

>Here are some of the questions I need to discuss with you,

>Nicole

>----Original Message-----

>From: Dolly Vance [mailto:dvance@flehr-iplaw.com]

>Sent: Friday, August 20, 1999 1:42 PM

>To: nverona@rigel.com

>Subject: info

>Dear Nicole,

>Hope you're well. Here's a complete list of what I am missing from the

>initial 9 disclosures.

- >1) The names of binding partners (if any actual) for CAH and >tankyraseH.
- >2) The nucleic acid and amino acid sequences for PAN and TNIK >(actually, all figures that go with the manuscript for TNIK).
- Please confirm that R0101 and PP5 are NOT novel, and that all >others are novel.

>Thanks. Dolly

>P.S. I understand your hours are reduced. Any chance you can give me a time frame for providing the above information? Thanks again, Dolly



FLEHR, HOHBACH, TEST ALBRITTON & HERBERT

1999 OCT - 1 AM 10: 05

RECEIVED

Exhal # 09/843 149

September 30, 1999

Ms. Dolly Vance Flehr, Hohbach, Test, Albritton and Herbert LLP 4 Embarcadero Center, Suite 3400 San Francisco, California 94111-4187

Dear Dolly,

Enclosed are documents pertaining to the cell-cycle patent applications that you requested.

The documents include:

- 1. TankyraseH abstracts involving TRF, P21, and PARP
- 2. TankyraseH nucleotide sequence alignment report
- 3. TankyraseH amino acid sequence alignment report
- 4. R0101 figures with corrected CDK 2, 3, and 4 labels
- 5. Mkinase nucleotide and amino acid sequences with its kinase domain and nuclear localization sequence (NLS) highlighted

Additional information will be sent to you next week.

Please call or email me if you have any questions.

Sincerely,

Nicole Verona

240 East Grand Avenue South San Francisco, CA 94080 Main phone: 650.624.1100 Fax: 650.624.1101 http://www.rigel.com